REMARKS

Claims 21-36 are pending in the application. It is noted that the Examiner has not appeared to examine claim 36; however, since claim 36 is dependent from claim 26, all arguments provided in this Amendment with respect to claim 26 are applicable. Additionally, the applicant reserves the right to present any additional arguments or amendments should the Examiner make additional comments concerning claim 36.

Claims 22, 29 and 35 have been amended. No new matter is added by these amendments.

I. Objection to the Specification.

At numbered paragraph 4 of the Office Action, the Examiner has objected to the specification as failing to provide a proper antecedent basis for the claim language "plurality of microspheres."

The applicant contends that this objection is unfounded. The specification makes clear that in one embodiment, the claimed composition includes a plurality of microspheres. *See, e.g.*, page 5, lines 3-4 ("In a second embodiment of the invention, the bioadhesive material is a plurality of microspheres."); *see also,* claim 5 as originally filed ("A drug delivery composition according to claim 1 wherein the bioadhesive material is a plurality of microspheres.").

Accordingly, it is submitted that the specification supports this term. The reconsideration and withdrawal of the objection is requested.

II. Objections Under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected claims 21-35 under 35 U.S.C. § 112, first paragraph contending that the specification does not contain a written description of the claimed invention in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventors had possession of the invention at the time the application was filed. These rejections are traversed in part. The specific grounds that underlie the Examiner's rejections are discussed below with particularity.

The Examiner contends that the phrase "about 0.1% to 50%" is not supported by the specification.

The claims have been amended to delete the term "about." Therefore it is submitted that this rejection is no longer applicable.

The Examiner contends that the "concentrations of ICAM-1 recited in microsphere formulation, namely 0.1% to 50% (claims 22, 29) and "1% to 20% (claims 23 and 30)," are not supported by the specification. The applicant disagrees.

As is described in the specification, the composition of the invention includes several embodiments. One of these embodiments is a formulation in which the bioadhesive material is a plurality of microspheres. Spec. at page 5, lines 3-4. The application describes the numerous materials from which the microspheres can be made.

> The microsphere can be prepared from a suitable material such as ***starch***, starch derivatives, amylodxtrin, amylopectin and cross-linked variants thereof, ***gelatin***, albumin, ***alginate***, ***gellan***, ***hyaluroinic acid***, ***chitosan***, dextran and dextran derivatives.

Spec. at page 5, lines 6-9 (emphasis added).

The specification further discloses that the <u>microsphere formulation</u> (composed of microspheres prepared of any of the listed materials in the specification), may have an ICAM-1 concentration of 0.1% to 50% (as recited in claims 22 and 29) or 1% to 20% (as recited in claims 23, 30).

> The content of ICAM in the microsphere formulation is preferably in the range 0.1% to 50% w/w, more preferably 0.5% to 25% and most preferably 1% to 20% w/w.

Spec. at page 8, lines 23-25.

While the Examiner has listed these claims as being rejected under 35 U.S.C. § 112, first paragraph, he has failed to provide specific grounds for the rejection of claims 21, 28 and 36. However, the applicants point out that each of these claims is directed to a drug delivery composition that comprises a (i) chitosan solution and (ii) ICAM wherein the ICAM is present in a concentration of 0.01% to 20% by weight per volume (claims 20 and 36) or 0.2% to 5% weight per volume (claims 21 and 28). Support for these recitations is found in the specification at, *e.g.*, page 4, 26-29.

> The ICAM-1 is preferably mixed with a chitosan solution in concentrations in the range of 0.01% to 20% w/v, ... and more preferably 0.2% to 5% w/v.

Spec. at 4, lines 26-29.

The Examiner contends that the language "which composition adheres to the epithelia and/or mucosal surface of the nasal cavity" is not supported by the specification. The applicant disagrees.

It is well settled that under 35 U.S.C. § 112, the initial disclosure need not contain a verbatim recitation of the precise words used in the claims. It is enough that the subject matter to which the questioned language is directed is conveyed in the specification to a person of skill in the art such that this person would have understood that the applicant was in possession of the invention at the time of filing. In the present situation, it is clear throughout the specification as originally filed that the drug composition is intended to be administered intranasally and that one of the advantages of the composition is that it adheres to the interior of the nasal cavity. *See, e.g.*, specification at page 3, lines 11-15 ("the present invention therefore provides a drug delivery composition for nasal administration comprising ... a bioadhesive material. We use the term "bioadhesive" to include a material that adheres to the nasal mucosa ... .") "The adhesion may take place to the epithelial (cellular) surface or to the mucus overlying that surface. Thus, as a person of ordinary skill would understand that the words "epithelial (cellular) surface" and "epithelia" are the same and that mucus overlying the epithelial surface and mucosal surface convey the same subject matter. It is submitted, therefore, that a person of ordinary skill in the art would have understood that the applicant was in possession of the invention at the time the application was filed.

The Examiner has asserted that the language reciting "chemical or physical bonds in claim 28." or, *e.g.*, 27 and 35 is not supported in the specification. In each instance is supported by a disclosure in the specification as initially filed. As discussed above, a bioadhesive is defined in this application as a "chitosan solution" (Spec. at page 3, lines 29-30) and/or a "plurality of microspheres" (page 5, lines 3-4). The specification as filed further defines a bioadhesive as that which adheres to the interior of the nasal cavity using the chemical and mechanical attachments described in claims 27 and 35.

> We use the term "bioadhesive" to include a material that adheres to the nasal mucosa by chemical or physical bindings such as Van der Waals interaction, ionic interaction, hydrogen bonding or by polymer chain entanglement. The adhesion may take place to the epithelial (cellular) surface or to the mucus overlying that surface.

Spec. at page 3, lines 14-18.

In view of the foregoing, it is submitted that the Examiner's rejections under 35 U.S.C. § 112, first paragraph, are inapplicable and should be withdrawn. Each of the claim elements called out by the Examiner describe subject matter which is disclosed verbatim and/or in terms well understood to a person of skill in the art such that that person would have understood that the applicant was in possession of the invention as presently claimed at the time the application was filed.

Reconsideration and withdrawal of these rejections is respectfully requested.

III. Objection to Claims.

The Examiner has objected to claim 22 for missing punctuation and a repetitive recitation. These two typographical errors have been corrected by amendment of claim 22.

Claim 35 is objected to because of a spelling error. This error has been corrected by amendment to claim 35.

Respectfully, it is submitted that the Examiner's objections are no longer applicable. Reconsideration and withdrawal is requested.

IV. Rejection Under 35 U.S.C. § 103(a).

The Examiner has rejected claims 21-35 under 35 U.S.C. § 103(a) as being unpatentable over combination of eight references for reasons set forth in prior Office Actions. Specifically, the Examiner contends that the claims are obvious over the disclosure of:

(i) U.S. Patent No. 5,482,706 of Igari *et al.* ("Igari");

(ii) U.S. Patent No. 5,589,453 of Greve *et al.* ("Greve");

(iii) U.S. Patent No. 5,730,983 of Wegner *et al.* ("Wegner");

(iv) U.S. Patent No. 5,422,907 of Gwaltney *et al.* ("Gwaltney");

(v) U.S. Patent No. 5,707,644 of Illum ("Illum '644");

(vi) U.S. Patent No. 5,690,954 of Illum ("Illum '954"); and

(vii) Kublick *et al.*, Eur. J. Pharm. Biopharm. 39:192-196, 1993 ("Kublick").

The applicant respectfully traverses the rejection. The applicant's argument is set forth in its response dated February 5, 2004, will not be repeated in detail. However, the applicant's prior comments are incorporated herein by reference. The applicant reiterates that no combination of the seven prior art references cited by the Examiner establishes a *prima facie* case of obviousness. No combination of the references teaches or suggests all elements of the invention. With respect to the composition of the invention, the combination of the references lacks disclosure of (1) a composition that includes a chitosan solution and ICAM (claims 20, 21), (2) a composition that includes a plurality of microspheres of the recited materials and ICAM-1 (claims 23-25), and (3) an ICAM-1 composition that is adapted to be adhered to the epithelial and/or mucosal surface of the nasal cavity.

With respect to the method claims of the invention, any combination made of the cited prior art references lacks at least disclosure of: (i) a method of treating a viral infection affecting the nasal cavity including adhering an antivirally effective amount of the recited composition to the epithelial and/or mucosal surface of the nasal cavity (claims 26-36); (ii) using an ICAM-1 composition that includes the recited bioadhesives (chitosan solution and microspheres of specific materials) (claims 26-36); and (iii) a method of improving the retention of an ICAM-1 composition in the nasal cavity (claims 34 and 35). Igari and Greve, the primary references upon which the Examiner relies, do not teach use of a chitosan solution in their disclosed compositions. The base materials in Igari are taught as being formed into solid, not liquid dosage forms. Moreover, no disclosure of the microspheres of the recited materials (starch, chitosan, gelatin, gellan, hyaluroinic acid, or alginate) is provided. Moreover, Igari is lacking any disclosure of microspheres made of the recited materials and adhesives of the composition to the epithelial and/or mucosal surface of the nasal cavity.

Greve is a basic science reference in that no specific practical applications, pharmaceutical or otherwise are taught or suggested. Greve teaches that ICAM used in the basic science experiments can be used to halt infection of a cell in culture by the virus. However, these cells are not in a nasal cavity, nor is a method of treatment taught or suggested in Greve. Greve does not address in any manner whether ICAM-1 can be formulated into an excipient or carrier substance for administration to any multicellular living being for therapeutic purposes.

Greve does not discuss use of chitosan solution at all. Indeed, Greve does not even teach or suggest that the ICAM disclosed therein can be formulated into any type of pharmaceutical composition or chitosan solution. Finally, as the Examiner himself has conceded, Greve does not discuss use of microspheres as recited. Greve does not teach or suggest methods for administering ICAM-1 to the nasal cavity so that the retention of the ICAM-1 in the nasal cavity shall be improved.

None of the other references as combined by the Examiner can fill these voids in the disclosures of Igari and Greve. Neither Wegner, Gwaltney, the Illum references, or Kublick discloses the chitosan solution, and this deficiency of claim element in the Examiner's combination remains unremedied. None of the remaining references teaches adherence of the ICAM-1 composition to the epithelial and/or mucosal surface of the nasal cavity or use of microspheres of the recited materials (starch, chitosan, gelatin, gellan, hyaluroinic acid, or alginate, and ICAM-1). One group does not teach use of a chitosan solution or microspheres of the recited materials. Moreover, Wegner teaches application of the Wegner composition to the epithelia of the lungs, not adherence of the composition to the epithelial and/or mucosal surface of a nasal cavity, where it is well known that a specific physiological process which consistently monitors and clears the nasal passages is in effect.

Similarly, the disclosures of Gwaltney, the Illum references, and Kublick lack a teaching of an ICAM composition that includes a chitosan solution. Moreover, they additionally do not disclose adherence of the composition to the epithelial and/or mucosal surfaces of the nasal cavity.

Additionally, the Examiner has failed to demonstrate that a person of skill would have been motivated to make the combination suggested by the Examiner. A person of skill in the art would have had not motivation in the art to make any of the combinations suggested by the Examiner, nor would he have had a reasonable expectation that the combination would give rise to a successful composition for nasal administration of ICAM-1 to the nasal cavity. Greve makes no disclosure of any pharmaceutical composition or *in vivo* pharmaceutical use of ICAM-1. None of the remaining references cited by the Examiner addresses the difficulty in preparing a composition that allows for administration of an active agent to a nasal cavity. Gwaltney, the Illum references, and Kublick each teach compositions that are adapted for transport of the active agent via the nasal route in the blood stream. Wegner is expressly designed to administer the

ICAM containing composition to the endothelial cells of the lung, via any feasible administration route, including oral or nasal routes. Accordingly, a person seeking to prepare a composition which is adapted to deliver an anti-virally effective amount of ICAM-1 to the nasal cavity would not rely upon, or combine the teachings of, references directed to compositions which facilitate systemic administration of a drug or active agent, as do the cited references. Further, given these teachings, it is unlikely that a person of skill would have had a reasonable expectation of success.

The Examiner appears to have not considered the applicant's argument because he characterizes the applicant's arguments as an individual attack on each of the references. While the applicant agrees that obviousness cannot be overcome by an assessment of individual references when it is based on a combination, the applicant has not done this. Tasked with the job of establishing a negative, *i.e.*, that the combination does not teach or suggest each element of the invention, the applicant must necessarily point out that each of the seven cited prior art references is lacking in a specific element, so that its contention that the combination of those references does not contain that specific element or elements, is not conclusory and unsupported. It is respectfully submitted that the Examiner cease characterizing the applicant's argument as one involving only "individual attack" and consider the argument for its substance, which demonstrates that the combination does not teach or suggest all elements of the invention.

In view of the foregoing arguments, it is respectfully submitted that the claims are patentably distinguishable over all cited prior art. Reconsideration and allowance of claims 20-36 is respectfully requested.

Respectfully submitted,

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